REMARKS

Claims 27-34 are pending.

In this submission, Applicants present additional references in support of Applicants' arguments. Applicants note that some of the references are provided in the form of full-text articles, while others are provided as abstracts. Applicants submit that the full-text articles are provided solely because they are available, and that Applicants do not intend to make any distinction among the references, or to indicate that some references are more pertinent or material than others.

Applicants respectfully traverse the present rejections.

35 U.S.C. § 101

Claims 27-34 stand rejected under 35 U.S.C. §101 as allegedly not supported by either an asserted utility that is specific and substantial or by a well-established utility. Specifically, the Office action alleges that "the Examiner has made a *prima facie* case that the mild amount of gene amplification (approximately 2 fold to 4 fold) of nucleic acids encoding the claimed protein are not indicative of an increased amount of protein." Page 3 of the Office action. The Office action acknowledges that Applicants have submitted significant evidence in rebuttal of the alleged *prima facie* case of lack of utility but rejects this evidence as insufficient to overcome the *prima facie* case. In particular, the Office action alleges that the second Polakis Declaration is not persuasive because it does not specifically address data for PRO347 or explain how the data presented therein compares to PRO347, including whether the same methodology was used, whether gene amplification levels were the same, or whether the controls were the same. The Office action also alleges that the references cited by Applicants are not persuasive because those references are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general.

Applicants respectfully disagree that these are sufficient bases for finding the evidence presented by Applicants unpersuasive. According to MPEP § 2107.02, "the applicant

does not have to provide evidence . . . such that it establishes an asserted utility as a matter of statistical certainty." Thus, it is not a legal requirement to establish a "necessary" correlation between an increase in PRO347 gene copy number and PRO347 protein expression levels. Instead, as discussed previously, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, if the totality of the evidence demonstrates that it is more likely than not that PRO347 gene amplification correlates with PRO347 polypeptide overexpression, that is sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

More specifically, **the totality of the evidence**, including arguments, declarations, and submitted references **must be considered** and a rejection for lack of utility ***cannot*** *properly be maintained if the totality of that evidence demonstrates that the asserted utility is more likely true than not true. See e.g., In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965), *Nelson v. Bowler*, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980), *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967), and *In re Chilowsky*, 229 F.2d 457, 462, 108 USPQ 321, 325 (CCPA 1956). Applicants submit that when the evidence is considered in its entirety, **as it must be**, it is clear that a correlation between PRO347 gene amplification and protein overexpression must be acknowledged.

The second Declaration of Paul Polakis is provided as evidence that in general, it is more likely than not that gene amplification correlates with protein overexpression. Therefore, regardless of whether the data described in the second Polakis Declaration and the gene amplification data for PRO347 are the same, and regardless of whether the same methodologies were used to obtain and analyze that data, the Polakis Declarations are persuasive evidence of how one of ordinary skill in the art would view Applicant's assertion of utility, which is based on the art accepted correlation between gene amplification and protein overexpression. Moreover, the data in the second Polakis Declaration is relevant to the expression pattern of PRO347 because PRO347 was identified through

Genentech's Tumor Antigen Project. Indeed, although the Polakis Declarations don't explicitly state this, the description of Genentech's Tumor Antigen Project in the Polakis Declarations and the description of identification of PRO347 in the specification are similar. Specifically, in the first and second Polakis Declarations, Dr. Polakis explains that one of his primary responsibilities:

> has been leading Genentech's Tumor Antigen Project, which is a large research project with a primary focus on identifying tumor cell markers that find use as targets for both the diagnosis and treatment of cancer in humans. . . . The primary purpose of this research is to identify proteins that are abundantly expressed on certain human tumor tissue(s) and that are either (i) not expressed, or (ii) expressed at detectably lower levels, on normal tissue(s).

Paragraphs 2 and 3 of the first and second Polakis Declarations. Similarly, at Example 28, pages 119-120, the present specification explains that:

> This example shows that . . . PRO347 . . . encoding genes are amplified in the genome of certain human lung, colon and/or breast cancers and/or cell lines. Amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers. . . . The starting material for the screen was genomic DNA isolated from a variety of cancers. . . . As a negative control, DNA was isolated from the cells of ten normal healthy individuals which was pooled and used as assay controls for the gene copy in healthy individuals (not shown). The 5' nuclease assay (for example, TaqMan™) and real-time quantitative PCR (for example, ABI Prizm 7700 Sequence Detection System™ (PerkinElmer, Applied Biosystems Division, Foster City, CA)), were used to find genes potentially amplified in certain cancers. The results were used to determine whether the DNA encoding . . . PRO347 . . is over-represented in any of the primary lung or colon cancers or cancer cell lines or breast cancer cell lines that were screened.

In addition, at paragraph 4 of the second Polakis Declaration, Dr. Polakis explains that through the Tumor Antigen Project, approximately 200 gene transcripts have been identified that are present in human tumor tissue at *significantly higher levels* than in normal human tissue." (emphasis added). Applicants previously submitted a declaration of Audrey Goddard, Ph.D., in which Dr. Goddard explained that a Δct value greater than 1 is significant. (Paragraph 7 of the Goddard Declaration). At Example 28, the specification reports that a majority of the tissue samples tested and listed in Table 9 have a Δct value greater than 1. Thus, the data for PRO347 indicates it is expressed at *significantly* higher

levels than in normal tissue, similar to the data in the second Polakis Declaration. When Applicants' assertion of utility for PRO347 is taken in view of the Polakis Declarations, it is clear that Applicants' assertion of utility for PRO347 is more likely than not true. That is all that is required.

While Applicants maintain that the evidence previously submitted is sufficient support for Applicants' assertion of utility, Applicants herein submit an additional declaration by Dr. Randy Scott (the "Scott Declaration"). Dr. Scott was a co-founder of Incyte Pharmaceuticals, Inc., the world's first genomic information business, and is currently the Chairman and Chief Executive Officer of Genomic Health, Inc., a life science company located in Redwood City, California, which provides individualized information on the likelihood of disease recurrence and response to certain types of therapy using gene expression profiling. Based on his more than 15 years of personal experience with the DNA microarray technique and its various uses in the diagnostic and therapeutic fields, and his familiarity with the relevant art, ***Dr. Scott unequivocally confirms that, as a general rule, there is a good correlation between mRNA and protein levels in a particular tissue***. As stated in paragraph 10 of the Scott Declaration:

> "One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. Although there are some exceptions on an individual gene basis, **it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue**. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, **without the need to directly measure individual protein expression levels.**" (emphasis added).

The conclusions of the Polakis I and II, and the Scott Declarations are further supported by the teachings within Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (herein after Cell 3rd) and (4th ed. 2002) (excerpts attached as Exhibit 1). Figure 9-2 of Cell 3rd shows the

steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Cell 3rd provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Cell 3rd at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Cell 3rd at 453 (emphasis added). Thus, as established in Cell 3rd, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Cell 4th, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Cell 4th at 302 (Emphasis added). Similarly, Figure 6-90 on page 364 of Cell 4th illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Cell 4th at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Cell 4th at 379 (Emphasis added). Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (copy enclosed under Exhibit 1) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (Emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004 (copy enclosed in Exhibit 1). Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" *Zhigang* at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." *Zhigang* at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." *Id.* at 7

Further, Meric *et al.*, Molecular Cancer Therapeutics, Vol. 1, 971-979 (2002) (a copy enclosed in Exhibit 1) states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (Emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the Declarations of Dr. Polakis and Dr. Scott, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

Applicants previously submitted references by Pollack, Orntoft, Bermont, Varis, Hu, Papotti, Walmer, Janssens, Hahnel, Kammoir, Maryuamo, Bea, and Futcher in further

support of this general, art recognized correlation. The Office action however, rejects this evidence because the references allegedly are directed to "analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general." Page 6 of the Office action mailed September 7, 2006. Applicants respectfully disagree that the previously submitted references do not demonstrate general trends. Although some references may focus only on a single gene or a few genes, numerous references have been cited. When that evidence is considered in its totality *as it must be*, that evidence shows a positive correlation between gene amplification and protein overexpression for the numerous *different* genes examined in the references cited. Therefore, contrary to the allegation in the Office action, this evidence *clearly* demonstrates a general trend of correlation across a *wide* variety of genes.

Further, in addition to the supporting references previously submitted, Applicants submit herewith further references as additional support for their assertion that, changes in DNA levels generally lead to corresponding changes in the level of the encoded polypeptide.

For example, in a study by Wang *et al.* (Urol. Res. 2000; 28(5):308-15) (abstract attached as Exhibit 2) the authors report that down-regulation of E-cadherin protein has been shown in various human tumors. *Id.* at Abstract. In the reported study, the authors examined the expression of cadherins and associated catenins at the mRNA level in paired tumor and nonneoplastic primary prostate cultures. They report that "[s]ix of seven cases of neoplastic cultures showed moderately-to-markedly decreased levels of E-cadherin and P-cadherin mRNA. Similar losses of alpha-catenin and beta-catenin mRNA were also observed." *Id.* As Applicants' assertion would predict, the authors state that the mRNA measures showed "good correlation" with the results from protein measures. The authors conclude by stating that "this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied." *Id.*

In a more recent study by Munaut *et al.* (Int. J. Cancer. 2003; 106(6):848-55) (abstract attached as Exhibit 3) the authors report that vascular endothelial growth factor (VEGF) is expressed in 64-95% of glioblastomas (GBMs), and that VEGF receptors (VEGFR-1, its soluble form sVEGFR-1, VEGFR-2 and neuropilin-1) are expressed predominantly by endothelial cells. *Id.* at Abstract. The authors explain that infiltrating tumor cells and newly-formed capillaries progress through the extracellular matrix by local proteolysis involving matrix metalloproteinases (MMPs). In the present study, the authors "used quantitative RT-PCR, Western blot, gelatin zymography and immunohistochemistry to study the expression of VEGF, VEGFR-1, VEGFR-2, sVEGFR-1, neuropilin-1, MT1-MMP, MMP-2, MMP-9 and TIMP-2 in 20 human GBMs and 5 normal brains. The expression of these MMPs was markedly increased in most GBMs with excellent correlation between mRNA and protein levels." *Id.* Thus, the results support Applicants' assertion that changes in mRNA level lead to corresponding changes in protein level.

In another recent study, Hui *et al.* (Leuk. Lymphoma. 2003; 44(8):1385-94 (abstract attached as Exhibit 4) used real-time quantitative PCR and immunohistochemistry to evaluate cyclin D1 mRNA and protein expression levels in mantle cell lymphoma (MCL). *Id.* at Abstract. The authors report that seven of nine cases of possible MCL showed overexpression of cyclin D1 mRNA, while two cases showed no cyclin D1 mRNA increase. *Id.* Similarly, "[s]ix of the seven cyclin D1 mRNA overexpressing cases showed increased cyclin D1 protein on tissue array immunohistochemistry; one was technically suboptimal." *Id.* The authors conclude that the study "demonstrates good correlation and comparability between measure of cyclin D1 mRNA ... and cyclin D1 protein." *Id.* Thus, this reference supports Applicants' assertion.

In a recent study by Khal *et al.* (Int. J. Biochem. Cell Biol. 2005; 37(10):2196-206) (abstract attached as Exhibit 5) the authors report that atrophy of skeletal muscle is common in patients with cancer and results in increased morbidity and mortality. *Id.* at Abstract. To further understand the underlying mechanism, the authors studied the expression of the ubiquitin-proteasome pathway in cancer patient muscle using a

competitive RT-PCR to measure expression of mRNA for proteasome subunits C2 and C5, while protein expression was determined by western blotting. "Overall, both C2 and C5 gene expression was increased by about three-fold in skeletal muscle of cachectic cancer patients (average weight loss 14.5+/-2.5%), compared with that in patients without weight loss, with or without cancer. ... There was a good correlation between expression of proteasome 20S alpha subunits, detected by western blotting, and C2 and C5 mRNA, showing that increased gene expression resulted in increased protein synthesis." These findings support Applicants' assertion that changes in mRNA level lead to changes in protein level.

Support for Applicants' assertion is also found in an article by Caberlotto *et al.* (Neurosci. Lett. 1999; 256(3):191-4) (abstract attached as Exhibit 6). In a previous study, the authors investigated alterations of neuropeptide Y (NPY) mRNA expression in the Flinders Sensitive Line rats (FSL), an animal model of depression. *Id.* at Abstract. The authors reported that in the current study, that NPY-like immunoreactivity (NPY-LI) was decreased in the hippocampal CA region, and increased in the arcuate nucleus, and that fluoxetine treatment elevated NPY-LI in the arcuate and anterior cingulate cortex. The authors state that "[t]he results demonstrate a good correlation between NPY peptide and mRNA expression." Thus, increases and decreases in mRNA levels were reflected in corresponding changes in protein level.

Misrachi and Shemesh (Biol. Reprod. 1999; 61(3):776-84) (abstract attached as Exhibit 7) investigated their hypothesis that FSH regulates the bovine cervical prostaglandin E(2) (PGE(2)) synthesis that is known to be associated with cervical relaxation and opening at the time of estrus. *Id.* at Abstract. Cervical tissue from pre-estrous/estrous, luteal, and postovulatory cows were examined for the presence of bovine (b) FSH receptor (R) and its corresponding mRNA. The authors report that bFSHR mRNA in the cervix was maximal during pre-estrus/estrus, and that the level of FSHR protein was significantly higher in pre-estrous/estrous cervix than in other cervical tissues. *Id.* The authors state that "[t]here was a good correlation between the 75-kDa protein expression and its corresponding transcript of 2.55 kb throughout the estrous

cycle as described by Northern blot analysis as well as RT-PCR." *Id.* Thus, changes in the level of mRNA for bFSHR led to corresponding changes in FSHR protein levels, a result which supports Applicants' assertion.

In a study by Stein *et al.* (J. Urol. 2000; 164(3 Pt 2):1026-30) (abstract attached as Exhibit 8), the authors studied the role of the regulation of calcium ion homeostasis in smooth muscle contractility. *Id.* at Abstract. The authors investigated the correlation between sarcoplasmic endoplasmic reticulum, calcium, magnesium, adenosine triphosphatase (SERCA) protein and gene expression, and the contractile properties in the same bladder. Partial bladder outlet obstructions were created in adult New Zealand white rabbits, which were divided into control, sham operated and obstructed groups. Stein *et al.* report that "[t]he relative intensities of signals for the Western [protein] and Northern [mRNA] blots demonstrated a strong correlation between protein and gene expression. ... The loss of SERCA protein expression is mediated by down-regulation in gene expression in the same bladder." *Id.* This report supports Applicants' assertion that changes in mRNA level, *e.g.,* a decrease, lead to a corresponding change in the level of the encoded protein, *e.g.,* a decrease.

In an article by Gou and Xie (Zhonghua Jie He He Hu Xi Za Zhi. 2002; 25(6):337-40) (abstract attached as Exhibit 9) the authors investigated the expression of macrophage migration inhibitory factor (MIF) in human acute respiratory distress syndrome (ARDS) by examining the expression of MIF mRNA and protein in lung or colon tissue in ARDS and normal persons. *Id.* at Abstract. The authors report "undetectable or weak MIF mRNA and protein expression in normal lung or colons. In contrast, there was marked upregulation of MIF mRNA and protein expression in the ARDS lung or colons." *Id.* This is consistent with Applicants' assertion that a change in mRNA for a particular gene, *e.g.,* an increase, generally leads to a corresponding change in the level of protein expression, *e.g.,* an increase.

These studies are representative of <u>numerous</u> published studies which support Applicants' assertion that changes in mRNA level generally lead to corresponding

changes in the level of the expressed protein. In addition to these supporting references, Applicants also submit herewith additional references which offer support of Applicants' asserted utility. For example, in a study which is closely related to Applicants' asserted utility, Godbout *et al.* (J. Biol. Chem. 1998; 273(33)21161-8) (abstract attached as Exhibit 10) studied the DEAD box gene, DDX1, in retinoblastoma and neuroblastoma tumor cell lines. The authors report that "there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied." *Id.* Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Van der Wilt *et al.* (Eur. J. Cancer. 2003; 39(5):691-7) (abstract attached as Exhibit 11) studied deoxycytidine kinase (dCK) in seven cell lines, sixteen acute myeloid leukemia samples, ten human liver samples, and eleven human liver metastases of colorectal cancer origin. *Id.* at Abstract. The authors report that "enzyme activity and protein expression levels of dCK in cell lines were closely related to the mRNA expression levels" and that there was a "good correlation between the different dCK measurements in malignant cells and tumors." *Id.*

Grenback *et al.* (Regul. Pept. 2004; 117(2):127-39) (abstract attached as Exhibit 12) studied the level of galanin in human pituitary adenomas using a specific radioimmunoassay. *Id.* at Abstract. The authors report that "[i]n the tumors analyzed with in situ hybridization there was a good correlation between galanin peptide levels and galanin mRNA expression." *Id.*

Similarly, Shen *et al.* (Blood. 2004; 104(9):2936-9) (abstract attached as Exhibit 13) examined the level of B-cell lymphoma 2 (BCL2) protein expression in germinal center (GC) B-cells and diffuse large B-cell lymphoma (DLBCL). *Id.* at Abstract. The authors report that "GC cells had low expression commensurate with the low protein expression level" and that in DLBCL the level of BCL2 mRNA and protein expression showed "in general, a good correlation." *Id.*

Likewise, in an article by Fu *et al.* (Blood 2005; 106(13):4315-21) (abstract attached as Exhibit 14) the authors report that six mantle cell lymphomas studied "expressed either cyclin D2 (2 cases) or cyclin D3 (4 cases). " *Id.* at Abstract. "There was a good correlation between cyclin D protein expression and the corresponding mRNA expression levels by gene expression analysis." *Id.*

These examples are only a few of the many references Applicants could cite in rebuttal to the PTO's arguments. Applicants submit herewith approximately 100 additional references (abstracts attached as Exhibit 15) which also support Applicants' assertion in that they report a correlation between the level of mRNA and corresponding protein, contrary to the assertion of the PTO that mRNA and protein levels are not correlated.

In summary, Applicants submit herewith a total of more than 140 references, in addition to the declarations and references already of record, to support Applicants' asserted utility. These references support the assertion that in general, a change in DNA levels for a particular gene leads to a corresponding change in the protein levels.

As Applicants have previously acknowledged, the correlation between changes in DNA levels and protein levels is not exact, and there are exceptions. Indeed, the Office action cites several references as evidence that mRNA levels are not necessarily predictive of protein levels. Specifically, the Office action references Nagaraja, Waghry, Sagynaliev as evidence that changes in mRNA expression do not result in changes in protein expression. Pages 7-9 of the Office action mailed Sept. 7, 2006. Nagaraja, however, does not conclude that *no* correlation exists between amplified genes and overexpressed proteins. Instead, Nagaraja only recognizes, as cited by the Office action, that extrapolation of changes in transcription level to changes in protein level cannot ***always*** be made. Page 9 of the Office action, Nagaraja at p.2329. As discussed above, statistical certainty is not required, but rather it only must be more likely than not.

Similarly, Waghry also does not conclude that *no* correlation exists. Rather, Waghry notes that "[i]nterestingly, for most of the proteins identified, there was no appreciable concordant change at the RNA level." Waghry posits three explanations for the lack of concordance: (1) the 2-D gels do not reveal whether a particular gene is represented by more than one protein isoform; (2) a translational control, post-translation modification or other change in protein turnover due to DHT treatment occurred; or (3) there is a lag time for changes at the RNA level to be reflected in a protein change. Based on this, Waghry concludes that "monitoring gene expression at both RNA and protein levels may provide complementary information that could not be ascertained by solely measuring RNA or protein." Waghry at 1332, second column, last paragraph (emphasis added). Thus, Waghry does not establish that it is more likely than not that there is no correlation between gene amplification and protein overexpression. Indeed, Waghry offers three reasons why concordance may not have been observed in this study. At best, Waghry teaches that gene amplification does not correlate with protein overexpression in every situation. But such a high level of correlation is not required; the correlation only has to be more likely than not.

Sagynaliev is an article on database mining to gather information on CRC gene and protein expression levels in various reported studies. Although Sagynaliev reports that it is difficult to reproduce transcriptomics results with proteomics tools, Sagynaliev acknowledges that this difficulty may be based on discrepancies in the sample populations (the reviewed transcriptomics studies involved 144 patients while the proteomics studies involved only 11 patients) and high impact publications being conducted on samples of only 2 patients. Thus, Sagynaliev does not make it more likely than not that no correlation exists between gene amplification and protein overexpression.

Similar to Nagaraja, Waghey and Sagynaliev, the other references cited in the Office action do not conclude that no correlation exists between gene amplification and protein overexpression. For example, Lilley teaches that extrapolations of correlation between transcript and protein level *cannot always* be made; Wildsmith only acknowledges that

gene expression data from a microarray *may* differ from protein expression data; King only establishes that mRNA levels *do not necessarily correlate* with protein levels; and Madoz-Gurdipe only concludes that for most published studies, it is *unclear how well* RNA levels reported correlate with reported protein levels. Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in DNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

Further, Applicants respectfully maintain that absolute certainty is not required. Specifically, statistical certainty regarding an Applicants' assertion of utility is not required to satisfy 35 U.S.C. § 101. *Nelson v. Bowler,* 626 F.2d 853, 856-857, 205 USPQ 881, 883-884 (CCPA 1980). Moreover, where an Applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed as "wrong" even where there may be some reason to question the assertion. MPEP § 2107.02. Rather, a 35 U.S.C. § 101 rejection should only be sustained where the asserted utility violates a scientific principle or is *wholly* inconsistent with contemporary knowledge in the art. *In re Gazave,* 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (emphasis added).

Thus, even if the references relied on by the Office action provide evidence of some instances where gene amplification does not correlate with protein overexpression these references alone do not demonstrate that the asserted utility violates a scientific principle, is wholly inconsistent with contemporary knowledge in the art, or make it more likely than not that a correlation between gene amplification and protein overexpression does not exist. Indeed, this is particularly true when the evidence is considered in its totality, as it must be. Specifically, the ample evidence submitted and relied on by Applicants, including the Scott, Polakis, and Goddard Declarations, and the numerous references discussed in

the responses previously submitted including Pollack, Orntoft, Hyman, Bermont, Varis, Hu, Papotti, Walmer, Janssens, Hahnel, Kammori, Bea, Maruyama, and Futcher, as well as the references discussed herein, including Wang, Munaut, Hui, Khal, Caberlotto, Misrachi and Shemesh, Stein, Gou and Xie, Godbout, Van der Wilt, Grenback, Shen, and Fu, clearly demonstrates that instances when gene amplification does not correlate with protein overexpression are the exception and not the rule. The declarations submitted by and references cited by Applicants clearly establish that the contemporary knowledge in the art agrees with the scientific principle that gene amplification correlates with protein overexpression.

For the reasons given above, Applicants respectfully submit that consideration of the totality of the evidence clearly demonstrates that Applicants' asserted utility is specific, substantial, and credible. Applicants have overcome this ground of rejection and respectfully request it be withdrawn.

35 U.S.C. § 112 ¶ 1, Enablement-Utility

Claims 27-34 stand rejected under 35 U.S.C. § 112 ¶1, because it is alleged that the presently claimed invention is not supported by a substantial utility, and therefore, one skilled in the art would not know how to use the claimed invention. As discussed in the remarks above, addressing the rejection under 35 U.S.C. § 101 for lack of utility, Applicants respectfully submit that the claimed polypeptide is supported by a substantial utility. Thus, Applicants respectfully request the Examiner reconsider and withdraw this ground of rejection.

SUMMARY

Applicants believe that currently pending Claims 27-34 are patentable. The Examiner is invited to contact the undersigned attorney for Applicants via telephone if such communication would expedite allowance of this application.

Respectfully submitted,

C. Noel Kaman

C. Noel Kaman
Registration No. 51,857
Attorney for Applicant

BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, ILLINOIS 60610
(312) 321-4200